NMR: Diagnostic Wave of the Future

SINCE ITS DISCOVERY in the 1940's, nuclear magnetic resonance (NMR) has been used by scientists to determine the molecular structure of chemical specimens. But only recently has NMR been applied to study the biochemistry of intact organs and to image various parts of the body. Despite the newness of the technology to medicine, applications foreign to existing technologies are already evident. By depicting the concentration, chemical form and spatial distribution of sensitive atomic nuclei, NMR is able to define body constituents and chemistry directly but noninvasively. Existing diagnostic technology defines structure (ultrasonography and radiography) or relies on injection of foreign substances to evaluate function or metabolism (angiography and radiotracer studies). With the use of NMR, atomic nuclei and chemical species can be studied directly. Thus, inferences about tissue health need not be made by looking at indirect functions such as radiographic attenuation or radiotracer distribution. Moreover, it is possible that NMR approaches will create an even greater diagnostic window by eliciting information analogous to that obtained by radiographic and radiotracer means through the use of metabolic or flow "tracer" chemicals.

The diagnostic potential of NMR is shown in part by a brief description of a few of the medically relevant sensitive nuclei: phosphorus 31, sodium 23, carbon 13 and hydrogen 1 (proton). ^{31}P, ^{23}Na and ^{13}C all have NMR sensitivities many times less than hydrogen. In vitro, ^{31}P NMR spectroscopy has been used to monitor the concentration of adenosine triphosphate, creatine phosphate and inorganic phosphate.[1] Each phosphate has a characteristic spectral position separate from the others. This separation is referred to as a chemical shift. With in vitro spectroscopy studies such as NMR it is possible to directly evaluate high-energy phosphate metabolism. In addition, the chemical shift position of the inorganic phosphate peak is related to pH and can be used to measure intracellular pH. Recently, Brown and co-workers[2] reported the feasibility of imaging chemical shift phosphate peaks in biologic concentration. In this way NMR can provide in vivo assessment of the effect of disease on intracellular biochemistry.

Sodium is abundant in extracellular fluid. Because of the substantially higher concentration of sodium in blood compared with its concentration in cells, sodium may be useful as a "blood pool" imaging agent. In fact, DeLayre and associates[3] recently published gated cardiac blood pool images of an isolated perfused beating rat heart using a spectrometer modified to produce images. Also, it is possible that intracellular leakage of sodium associated with damage to the cell membrane could be detected by NMR.

In contrast with ^{31}P and ^{23}Na, which represent nearly all of the phosphorus and sodium found in nature, ^{13}C represents only 1 percent of natural carbon. As such, it may be useful as an NMR tracer for evaluation of perfusion and metabolism. For example, precursors tagged with ^{13}C can be used to trace hepatic glycogen metabolism.[4]

The connection between the laboratory work and clinical application may be made by either topical magnetic resonance (TMR) or imaging. TMR is a highly innovative approach that generates NMR spectra of sensitive nuclei in intact animals or in humans. In TMR a spectrum is derived by isolating a sensitive volume in the object being investigated. For example, Ross and colleagues,[5] using a forearm in human volunteers and in patients with McArdle's syndrome, did studies with TMR to evaluate phosphorus metabolism during aerobic and ischemic exercise. Intracellular pH determined from chemical shift analyses of the inorganic phosphate peak paradoxically rose during ischemic exercise, due to the suspected inability of the metabolism of patients with McArdle's syndrome to break down glycogen. Other interesting applications of TMR have been investigated by Radda and his colleagues.[6]

While NMR spectroscopy with in vitro and TMR approaches provides a new way of studying disease, NMR imaging can depict location and concentration of sensitive nuclei. Protons are thus far the only nuclei that have been used in intact animals and in humans to produce images. The reason is twofold. First, protons are abundant in tissue water. Second, protons are the most sensitive nuclei for NMR detection. The state of the art in proton imaging is presented in an excellent review in this issue by Davis and co-workers. Proton images mostly depict water distribution.

Since Lauterbur in 1973[7] recognized that images could be derived from NMR by encoding

spatial information using a magnetic field gradient, rapid advances have led to the ability to produce tomographic or three-dimensional images with resolution rivaling x-ray computerized tomography. In contrast with radiography, the intensity of proton NMR images is largely related to the concentration of protons in water and lipids. In addition, relaxation times (T1 and T2) can be emphasized on NMR images by manipulating the timing of the radiofrequency pulses.[8] These "relaxation times" are affected by the chemical environment and may provide additional clues to the presence of disease. For example, work at the Massachusetts General Hospital using an ischemic stroke model in cats showed that changes in the NMR image occur as early as two hours after ligation.[9] Other important potentials of proton NMR imaging include the ability to depict blood flow patterns and the application of contrast-enhancing agents, such as paramagnetic molecular oxygen.

The progress from Lauterbur's concept in 1973 to proton images of high quality in 1982, coupled with the development of TMR, suggests a progression ultimately to methods that allow in vivo mapping of biochemical markers of cellular disease such as the measurement of high-energy phosphate levels, intracellular sodium pools and NMR tracers labeled with ^{13}C. For NMR to achieve its full potential, there will have to be an alliance between technologic and medical research and among pathophysiologically, biochemically and structurally oriented practitioners. Indeed, the level of advancement that is necessary for knowledgeable NMR research and practice could lead to the evolution of a new discipline in medicine.

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Poison Control Centers—A Vital Community Resource

ON JULY 14, 1981, the state of California began spraying malathion over a wide area of northern California; on August 10, 1981, some 5,000 South San Francisco residents were evacuated after a silicon tetrachloride gas line ruptured; on September 2, 1981, there were 60,000 residents evacuated from downtown San Francisco after a polychlorinated biphenyl/methane gas explosion; on December 4 seven Laotians ate *Amanita phalloides* in Santa Rosa, California. In each of these toxic, or potentially toxic, circumstances, the San Francisco Bay Area Regional Poison Control Center was a focal information center for citizens, public and private agencies and the news media. These events vividly illustrate the expanding role of a poison control center and the importance of such a center as a vital community health resource.

Pediatricians and local health departments began organizing poison control centers in the early 1950's. These early centers attempted to provide information and referral as well as preventive programs for poisoning. Lovejoy and his colleagues[1] from Boston summarized the growth of poison centers in 1979. The experience of the Massachusetts Poison Control Center emphasized the importance of establishing regional poison control services in many states and showed that 45,000 calls handled during 1978 cost $4 a call and were cost effective in decreasing the number of emergency room visits.[1]

It is estimated that there are approximately 5 million accidental and deliberate poisonings per year, with approximately 5,000 deaths. As an accidental cause of death, poisonings are surpassed only by motor vehicle accidents, drowning and burns.[2] The expanding poison center activities provide vital links for health care services. There are currently some 650 poison centers in the United States, which are unevenly distributed. In California there are now three centers certified by the American Association of Poison Control Centers (Sacramento, San Diego and San Fran-